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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/255,963 02/23/99 MA

P UM-03646

EXAMINER

HM22/0410

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ART UNIT

PAPER NUMBER

1633

DATE MAILED:

04/10/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

# Office Action Summary

Application No.

09/255,963

Applicant(s)

MA, PETER X.

Examiner

Sumesh Kaushal

Art Unit

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 01/16/01.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-20 and 22-44 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-20 and 22-44 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

## Attachment(s)

- 15) ☐ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_

- 18) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other:

### DETAILED ACTION

Applicant's response filed on 01/16/01 have been fully considered but is found unpersuasive for the reasons of record as set forth in the earlier office action (Paper No.8, 09/11/00). Claim 21 is canceled. Claims 1-2, 22-23, 31, 33-34 are amended and newly filed claims 39-44 are entered. Claims 1-20 and 22-44 are pending

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Claim Rejections - 35 USC § 112*

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:  
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 and 23-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims are drawn to method of making three dimensional cross-linked hydrogel system, wherein the hydrogel system is controlled to a predetermined size by varying a calcium ion concentration of a medium into which the hydrogel system is introduced.

Claims 1, 2 and 23 are indefinite because it is unclear how the variation in calcium ions alone controls a predetermined size of the hydrogel system. The shape and size of any hydrogel formed is the function of three-dimensional structure of the container into which the reaction is performed. Furthermore, the variation in calcium ions concentration only affects the gel size by gel shrinkage due to inter-molecular cross-linking reaction after the hydrogel is formed.

(specification, page 14 line13-22). Therefore, it is unclear whether the size as claimed is determined by the container dimensions to a larger extent or by gel shrinkage to smaller extent.

***Claim Rejections - 35 USC § 102***

Claims 1, 3-7, 9, and 23-28 stand rejected under 35 U.S.C. 102(a) as being anticipated by Draget et al (Carb. Poly. 14:159-178, 1991, *ref. of record*) for the same reasons of record as set forth in the official action mailed on 09/11/00.

The applicant argues that claims have been amended to include the step of selectively controlling the hydrogel system by varying the calcium ion/cation concentration of a medium into which the hydrogel system is introduced (response, page 6, para. 2) The applicant concluded that none of the cited references teach or suggest selective size control of hydrogel system by varying cation concentration in medium (response, page 6, para. 3).

However, this is found unpersuasive because Draget et al teaches the formation of a gel consisting of mixing 15mM  $\text{CaCO}_3$  with sodium alginate solution, then adding 30mM GDL, resulting in a final gel of pH 7 (see, e.g., pg 161, para. 2) just to avoid formation of acidic gels (page 163, para.3). Draget et al also teach that the sodium alginate can be substituted with alginate derived from *Marocystis pyrifera* or *Laminaria hyperbores*, thus altering the viscosity of the gel (pg 161, Table 1; pg 173); and that the dimensions of the gel (e.g. thickness and diameter) are largely a function of the dimensions of the mold into which they form, and can thus be easily modified by one of ordinary skill in the art. Furthermore, maximum gel strength was reached when  $\text{Ca}^{2+}$  concentration was equivalent to the amount of guluronic acid residues and syneresis become prominent when the calcium contents exceeded this value (page 175, fig-13, page 177 para.3). Therefore, the invention as claimed is clearly anticipated by the cited art, which teaches that variation in calcium ion concentration results in the formation of hydrogels with distinct characteristics.

*Claim Rejections - 35 USC § 103*

Claims 2, 8, 10-20, 22, 29-44 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Draget et al (Carb. Poly. 14:159-178, 1991) as applied to claims 1, 3-7, 9, and 23-28 above, and further in view of Hauselmann et al (US Patent 5,658,343) and Cao et al (Book of abstracts, BIOT-212, 211th ACS National Meeting, New Orleans 1996) *refs. of record*.

The applicant argues that claims have been amended to include the step of selectively controlling the hydrogel system by varying the calcium ion/cation concentration of a medium into which the hydrogel system is introduced to include cells incorporated into hydrogel composition (response, page 6, para. 2) The applicant further argues that none of the cited references teach hydrogel/cell system (response, page 7, para. 3). Thus, the applicant concluded that invention as claimed is not anticipated taught or rendered obvious by Drat, Cao or '343 either alone or in combination.

However, this is found unpersuasive because Draget et al teaches the formation of a gel consisting of mixing 15mM  $\text{CaCO}_3$  with sodium alginate solution, then adding 30mM GDL, resulting in a final gel of pH 7 (see, e.g., pg 161, para. 2) only to avoid formation of acidic gels (page 163, para.3). Draget et al also teach that the sodium alginate can be substituted with alginate derived from *Marocystis pyrifera* or *Laminaria hyperbores*, thus altering the viscosity of the gel (pg 161, Table 1; pg 173); and that the dimensions of the gel (e.g. thickness and diameter) are largely a function of the dimensions of the mold into which they form, and can thus be easily modified by one of ordinary skill in the art. Furthermore, maximum gel strength was reached when  $\text{Ca}^{2+}$  concentration was equivalent to the amount of guluronic acid residues and syneresis become prominent when the calcium contents exceeded this value (page 175, fig-13, page 177 para.3). Thus Draget clearly teaches that variation in calcium ion concentration results in the formation of hydrogels with distinct characteristics.

Furthermore, Hauselmann et al teach the method of producing an alginate gel in vitro comprising cells that produce an extracellular matrix, for implantation in vivo (e.g., col. 1, lines 39-60). Hauselmann et al also teach that the molar ratio of calcium ions to carboxyl groups in the gel determines the amount of crosslinking of the gel, as well as the amount of swelling and thus size of the gel (e.g, col 7, lines 29-46, & Figure 6a,b).

In addition, Cao et al teach the method of making and using biodegradable calcium alginate gels with osteoblasts in vitro for implantation in vivo to generate bone growth. The osteoblasts were suspended 1% sodium alginate, then 0.2g of  $\text{CaSO}_4$  was added to each ml of the admixt to initiate gel formation. The admixt was injected in nude mice, which results in the new bone formation in the transplanted animals (see abstract)

Therefore, in light of Draget, Hauselmann, and Cao et al teachings it would have been obvious to one of ordinary skill in the art to add cells, such as osteoblasts, to the composition disclosed by Draget. One would have been motivated to do this to utilize the gel as a scaffold for cell growth and differentiation, otherwise known as tissue engineering, both in vitro for implantation, or for injection and solidification in vivo, such as taught by Hauselmann and Cao. One would also have been motivated to alter the calcium ion concentration and the ratio of calcium ions to alginate carboxyl groups in order to alter the amount of  $\text{H}_2\text{O}$  binding to the matrix, and hence the amount of gel swelling and size of the gel, because Hauselmann et al disclose that this procedure is widely known and used in the art of hydrogels (e.g, Figure 6a,b). Therefore, the invention pertaining to specific ion concentrations and molar ratios resulting in hydrogel swelling and shrinking are result effective variables which could readily been determined by one of ordinary skill in the art.

### ***Conclusion***

No claims are allowed.


Application/Control Number: 09/255,963  
Art Unit: 1633

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Deborah Clark can be reached on (703) 305-4051. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Tracey Johnson, whose telephone number is (703) 308-0377. If the claims are amended canceled and/or added the applicants are advised to follow Amendment Practice under 37 CFR § 1.121 (<http://www.uspto.gov>).

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